40. (Newly added) The method of claim 5, wherein said monoclonal antibody is KKO.

Q6

41. (Newly added) The method of claim 14, wherein said monoclonal antibody is KKO.

REMARKS

The present invention relates to compositions, methods, and kits comprising a monoclonal antibody which is capable of binding with a PF4/heparin complex and shares key functional properties with polyclonal antibodies which participate in the pathogenesis of heparin induced thrombocytopenia/thrombosis (HIT/HITT).

Claims 1-39 are pending in the present application. Claims 7-11 and 15-39 were previously withdrawn from further consideration as being drawn to a non-elected invention. Thus, claims 1-6 and 12-14 are presently under consideration. New claims 40 and 41 have been added herein and are therefore also pending.

Sequence Listing

At page 2 of the Office Action, the Examiner asserts that the application fails to comply with the requirements of 37 C.F.R. 1.821 through 1.825 for the sequences disclosed, e.g., in figures 6A and 6B, as also set forth in the "Notice to Comply With Requirements For Patent Applications Containing Nucleotide Sequence and/or Amino Acid Sequence Disclosures supplied therewith.

In a good faith effort to expedite prosecution of the application, Applicants have added new SEQ ID NOs (see above) and provide herewith a substitute paper copy of the "Sequence Listing", an amendment directing its entry into the specification, a substitute copy of the "Sequence Listing" in computer readable form, and a statement that the content of the paper and computer readable copies are the same and include no new matter. Applicants have

also directed the entry of "SEQ ID NO" identifiers for every reference to the sequences in the specification.

Objection to the Specification and Rejection and Objection to Claims 1-6 and 12-14 pursuant to 35 U.S.C. § 112, first paragraph

At page 3, line 11, to page 6, line 7, the Examiner asserts that the specification fails to provide an adequate written description of the inventions and fails to provide an enabling disclosure because the specification does not provide evidence that the claimed biological materials are: (1) known and readily available to the public; (2) reproducible from the written description: or, (3) deposited in compliance with the criteria set forth in 37 CFR §§ 1.801-1.809. In the view of the Examiner, it is unclear if cell lines which produce antibodies having the exact chemical identity and properties of the antibody designated "KKO" are known and publicly available, or can be reproducibly isolated without undue experimentation. The Examiner also contends that it is the assertion of the Applicants that the sequences depicted in portions of Figures 6A and 6B are the sequences of the KKO antibody, yet the Examiner further contends that the sequences in Figure 6 are not those listed in Figure 7 (page 5, lines 4-8). In the view of the Examiner, it would require undue experimentation to reproduce the claimed monoclonal antibody species chemically as produced by the hybridoma designated "KKO" or any humanized derivative thereof. At page 5, lines 12-14, the Examiner then states that a suitable deposit of the hybridoma would satisfy the enablement requirements of 35 U.S.C. § 112, first paragraph.

Although not necessarily agreeing with the reasoning of the Examiner, in a good faith effort to expedite prosecution of the application, Applicants have agreed to deposit the hybridoma under the terms of the Budapest Treaty and a statement to that effect has been added to the specification by amendment. As soon as the ATCC Accession Numbers are available, Applicants will amend the specification further to include them. Applicants submit that the deposit will satisfy the requirements of 35 U.S.C. § 112 as stated by the Examiner at page 5, lines 12-14. Therefore, Applicants respectfully submit that the objection to the specification and rejection of claims 1-6 and 12-14 under 35 U.S.C. § 112, first paragraph, as

to availability of a cell line to the public have been overcome and request that the rejection be reconsidered and withdrawn.

Regarding the sequences of Figures 6 and 7, the differences in the first and last codons (and predicted amino acids) between the KKO heavy chain sequences in Figure 6 and Figure 7 are related to the PCR primers used to amplify the heavy chain gene segments (see Example 1). The primers used to amplify the KKO heavy chain segment for Figure 6 (SEQ ID NO:11) both lie outside of the coding region and thus the sequence depicted in Figure 6 represents the actual sequence of KKO as secreted by the hybridoma. The primers used to amplify the KKO heavy chain segment to be expressed as a recombinant protein, introduced certain insignificant mutations in certain residues to facilitate DNA cloning. Thus, the residues in Figure 7 are the ones in the recombinant form of KKO (see Examples 1 and 2 and Figures 1-8). Regarding the KKO light chain differences in Figure 6 (Figure 6B, upper panel, new SEQ ID NO:13) and Figure 7B (SEQ ID NO:3), it is known to those of skill in the art that a hybridoma may have more than one light chain and indeed KKO expresses two different light chains (SEQ ID NOs:3 and 13). As described above, SEQ ID NOs. have been provided for the sequences of Figure 6 (SEQ ID NOs:11-14) in order to comply with 37 CFR 1.821 to 1.825.

At page 6, lines 9-11 of the Office Action, the Examiner contends that the specification does not reasonably provide description of or enablement for any and every antibody population specific for PF4/heparin complexes other than monoclonal antibody KKO. The Examiner asserts that Applicants provide guidance only for KKO and provide no guidance as to what modifications or structures are important for the predictable function of another monospecific antibody. The Examiner also asserts that different structures may be found on antibodies with the same specificity, and that, conversely, similar structures may be found on antibodies having different specificities. It is also the view of the Examiner that in view of the guidance in the instant specification to a single species, the amount of experimentation required to determine functional structures or modifications for other usable species would be undue (page 7 lines 6-9).

Regarding the Examiner's rejection of claims 1-6 and 12-14 under 35 U.S.C. § 112, first paragraph, as lacking written description, Applicants respectfully traverse this rejection for the following reasons.

In *Vas-Cath, Inc. v. Mahurkar*, 19 USPQ2d 1111 (Fed. Cir. 1991), the Court of Appeals for the Federal Circuit traced the development of the written description requirement under 35 U.S.C. §112, first paragraph. The *Vas-Cath* Court, in a unanimous opinion, noted approvingly that in a written description analysis, "[t]he primary concern is factual and depends on the nature of the invention and the amount of knowledge imparted to those skilled in the art by the disclosure." *Vas-Cath*, 19 USPQ2d at 1116 (quoting *In re Wertheim*, 191 USPQ 90, 96 (C.C.P.A. 1976)). After discussing the policy reasons underlying the requirement, the Court set forth the standard for the written description requirement:

> The purpose of the "written description" requirement is broader than to merely explain how to "make and use"; the applicant must also convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. . . . The test for sufficiency of support in a parent application is whether the disclosure of the application relied upon "reasonably conveys to the artisan that the inventor had possession at that time of the later claimed subject matter."

Vas-Cath, 19 USPQ2d at 1117 (emphasis added) (quoting *Ralston Purina Co. v. Far-Mar-Co., Inc.*, 227 USPQ 177, 179 (Fed. Cir. 1985)). *Accord Regents of University of California v. Eli Lilly & Co.*, 43 USPQ2d 1398 (Fed. Cir. 1997), cited by the Examiner. Therefore, it is well-settled that the knowledge of those skilled in the art informs the written description inquiry.

Applicants respectfully submit that the claims reciting a composition comprising a monoclonal antibody which is capable of binding specifically with a PF4/heparin complex or humanized derivative thereof, or a method of making such antibodies, are supported by the specification as filed and satisfy the written description requirement of 35 U.S.C. § 112, first paragraph, under current law. Particularly, the claimed compositions comprising monoclonal antibodies capable of binding specifically with a PF4/heparin complex and specific sequences associated with nucleic acids and peptides encoded thereby are described by biological, chemical, and functional properties. For

Example, nucleic and amino acid sequences (SEQ ID NOs:1-4) are disclosed for a monoclonal antibody capable of binding specifically with a PF4/heparin complex (KKO) and one which cannot (RTO). Further disclosed are examples of biological acitvity, *e.g.*, capable of binding with a PF4/heparin complex, playing a role in activating platelets, and capable of binding with other PF4/glycosaminoglycan complexes. In addition, methods of making such antibodies and humanized derivatives thereof, and domains involved in PF4/heparin complex binding are disclosed, as are numerous assays for assessing the biological activity(ies). These properties more than satisfy the written description requirement and provide general biological activity characteristics to support any modifications or structures which are important for biological activity under 35 U.S.C. §112, first paragraph.

Applicants respectfully submit that each and every species, *e.g.*, each antibody capable of binding to a complex or a molecule or each nucleic acid sequence or each amino acid sequence of a peptide, need not be disclosed in order to satisfy the written description requirement. Indeed, in *In re Angstadt*, 190 USPQ 214, 218 (CCPA 1976), the court held that applicants "are not required to disclose every species encompassed by their claims even in an unpredictable art." Further, the cases cited by the Examiner do not support this conclusion for the reasons set forth below.

In *Regents of the Univ. of California v. Eli Lilly & Co.*, 43 USPQ2d 1398 (Fed. Cir. 1997), a case cited by the Examiner, a landmark case relating to written description in the context of amino and nucleic acids, the Court of Appeals for the Federal Circuit held that a description of the amino acid sequence of the A and B chains of human insulin did not provide a written description of human insulin cDNA where no part of the nucleic acid sequence of human insulin was disclosed. That is clearly not the case here where nucleic and amino acid sequences of two antibodies are disclosed (*i.e.*, one specific for PF4/heparin (KKO) and one which is not (RTO)), there has been extensive reduction to practice, where the binding domains mediating PF4/heparin binding have been identified, and where numerous assays for assessing that each antibody or derivative thereof has the desired biological activity are disclosed.

Further, the adequacy of the disclosure provided in the specification must be considered in light of the advanced state of knowledge in the relevant art and because there

has been extensive reduction to practice, *e.g.*, nucleic and amino acid sequences have been disclosed in the specification as filed as have numerous biological properties of the antibodies. Thus, the holding of *Regents of the Univ. of California v. Eli Lilly & Co.*, is inapposite under the present facts where there is extensive sequence data to provide ample written description of the subject matter of rejected claims 1-6 and 12-14. Indeed, the *Eli Lilly* Court, quoting *In re Angstadt*, 190 USPQ 214, 218 (CCPA 1976), recognized the long line of cases holding that applicants "are not required to disclose every species encompassed by their claims even in an unpredictable art." *Eli Lilly*, 43 USPQ2d at 1406.

Whatever the holding of *Regents of the Univ. of California v. Eli Lilly & Co.*, the case is not applicable under the facts under consideration herein, where the nucleic and amino acid sequences of monoclonal antibodies with or without the desired functional properties are disclosed, and where the specification as filed discloses numerous assays for determining if the antibody has the requisite biological activity(ies).

Therefore, the disclosure in the instant application clearly apprises one skilled in the art that Applicants were in possession of the claimed invention at the time the specification was filed for purposes of 35 U.S.C. §112, first paragraph. This is because the skilled artisan, to whom the application is addressed, armed with the teachings provided by the specification as filed and the knowledge of the prior art, would have reasonably understood that the invention encompasses a composition comprising a monoclonal antibody which is capable of binding specifically with a PF4/heparin complex, is capable of binding with other PF4/glycosaminoglycan complexes other than PF4/heparin, and is capable of activating platelets when PF4 and heparin are present. As noted previously elsewhere herein, the written description requirement must be analyzed in context of the knowledge of the skilled artisan, which in this case includes extensive sequence data disclosed in the specification as filed regarding nucleic acids encoding for KKO and RTO, and extensive knowledge in the art regarding production of mutants, variants, derivatives, and fragments of a protein of interest (*see, e.g.*, Wells, 1990, Biochem, 29:8509-8517; Ngo et al., 1994, In: The Protein Folding Problem and Tertiary Structure Prediction, pp. 492-495; Bork, 2000, Genome Research 10:398-400; Skolnick et al., 2000, Trends in Biotech. 18:34-39; Doerks et al., 1998, Trends in Genetics 14:248-250; Smith et al., 1997, Nature Biotech. 15:1222-1223;

Brenner, 1999, Tends in Genetics 15:132-33; Bork et al., 1996, Trends in Genetics 12:425-427) to identify antibodies having a desired biological activity, *e.g.*, binding PF4/heparin complexes and being involved in activating platelets, and where the region(s) involved in PF4/heparin binding have been identified. This is especially true where the specification provides extensive reduction to practice, including, but not limited to, working examples of the claimed nucleic acids and proteins encoded thereby, and numerous assays that can be used to identify additional monoclonal antibodies of the invention. Given the advanced state of the relevant art and the extensive disclosure provided by the specification as filed, claims 1-6 and 12-14 are amply supported and satisfy the written description requirement of 35 U.S.C. §112, first paragraph.

Applicants respectfully submit that the extensive disclosure and reduction to practice demonstrated by the specification as filed, provides ample written description for claims reciting a composition comprising a monoclonal antibody which is capable of binding specifically with at PF4/heparin complex, wherein said antibody preferentially binds with PF4/heparin relative to binding with either PF4 or heparin alone. The specification describes, for the first time, a monoclonal antibody which preferentially binds a PF4/heparin complex relative to either PF4 or heparin alone, that can bind other PF4/glycosaminoglycan complexes as well, and can activate platelets.

In sum, Applicants respectfully submit that the specification as filed amply supports claims reciting a monoclonal antibody or a humanized derivatized thereof which preferentially binds a PF4/heparin complex relative to either PF4 or heparin alone, that can also bind other PF4/glycosaminoglycan complexes as well, and can activate platelets, and the methods for making such an antibody. Further, Applicants respectfully submit that the skilled artisan would have understood, based upon the disclosure provided in the specification as filed, that the invention includes a monoclonal antibody or a humanized derivatized thereof which preferentially binds a PF4/heparin complex relative to either PF4 or heparin alone. That is, one skilled in the art would have understood, based on the extensive disclosure provided in the specification which provides, *e.g.*, nucleic and amino acid sequences of a monoclonal antibody or a humanized derivatized thereof which preferentially binds a PF4/heparin complex relative to either PF4 or heparin alone, nucleic acids encoding such an

antibody, where the protein domains have been identified that are involved in PF4/heparin and glycosaminoglycan binding, and where there were a plethora of protein modification methods well-known in the art for producing mutants, derivatives, and fragments, and extensive assays to assess whether a monoclonal produced possesses the requisite biological activity. Therefore, there is ample support in the specification as filed for claims reciting, *inter alia*, a monoclonal antibody or a humanized derivatized thereof which preferentially binds a PF4/heparin complex relative to either PF4 or heparin alone, and these claims satisfy the written description requirement of 35 U.S.C. §112, first paragraph.

At page 7, lines 7-18, the Examiner asserts that the amount of experimentation required to determine functional structures or modifications for other usable species would be undue. The Examiner also asserts that very different structures may be found on antibodies with the same specificity, and conversely, similar structure may be found on antibodies having different specificities and that one would no know, given the instant guidance and without further unguided experimentation, what variable region changes would predictably function in the invention other than those possessing both the intact V_H and V_L chains of the KKO antibody. It is also the view of the Examiner that the specification provides insufficient description and guidance to the functional structures of the KKO antibody and that an enabling disclosure for the preparation and use of only a few analogs or a product does not enable all possible analogs where the characteristics of the analogs are unpredictable, citing *Amgen Inc, v. Chugai Pharmaceutical Co. Ltd.* (18 USPQ 2d 1027 (CAFC 1991)). Applicants respectfully submit that claims 1-6 and 12-14 are enabled under 35 U.S.C. § 112, first paragraph and traverse this rejection for the following reasons.

It is well-settled that applicant need not have actually reduced the invention to practice prior to filing in order to satisfy the enablement requirement under 35 U.S.C. §112, first paragraph. MPEP §2164.02 (citing *Gould v. Quigg*, 822 F.2d 1074 (Fed. Cir. 1987)). Indeed, the invention need not contain a single example if the invention is otherwise disclosed in such manner that one skilled in the art will be able to practice it without an undue amount of experimentation (*In re Borkowski*, 422 F.2d at 908), and "representative samples are not required by the statute and are not an end in themselves" (*In re Robins*, 429 F.2d 452, 456-57, 166 USPQ 552, 555 (CCPA 1970)). Thus, 35 U.S.C. § 112, first paragraph, enablement does

not require any working examples.

The test of enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue. MPEP §2164.01 (citing *In re Angstadt*, 537 F.2d 498, 504 (C.C.P.A. 1976)). The fact that experimentation may be complex does not necessarily make it undue if the art typically engages in such experimentation. *Id.* Further, the specification need not disclose what is well-known to those skilled in the art and preferably omits that which is well-known to those skilled and already available to the public. MPEP §2164.05(a) (citing *In re Buchner*, 929 F.2d 660, 661 (Fed. Cir. 1991)). Therefore, under current law, enablement does not require a working example and experimentation is allowed so long as it is not undue.

Under the present patent law, claims 1-6 and 12-14, are enabled under 35 U.S.C. §112, first paragraph. The specification as filed amply supports these claims because the skilled artisan, armed with the methods disclosed in the specification, the nucleic and amino acid sequences of peptides comprising a monoclonal antibody capable of binding with a PF4/heparin complex and with a PF4/glycosaminoglycan complex other than PF4/heparin, and capable of activating platelets, and the methods of making such antibodies as provided by the disclosure in the specification as filed, would have been able to isolate and characterize, through routine experimentation, other monoclonal antibodies having the disclosed biological and biochemical activities as recited by the claims, and to practice the invention commensurate with the scope of the claims without undue experimentation.

Further, one of skill in the art would also be able to produce a variety of monoclonal antibodies capable of binding with PF4/heparin and playing a role in activating platelets, following the teachings set forth in the specification as filed and/or as known in the art based upon the disclosure provided in the specification without undue experimentation. That is, the crucial teachings of the invention, *inter alia*, discovery of a monoclonal antibody and that certain portions of the antibody bind with a PF4/heparin complex and that these antibodies are involved in activating platelets, and the methods for making such antibodies, are amply disclosed in the specification as filed (*see, e.g.*, pages 43-56, Examples 1-2, and Figures 1-8). Therefore, the application merely omits that which is well-known to those skilled in the art and already available to the public, *i.e.*, methods of identifying a monoclonal

antibody capable of binding with a specific complex, or having a specified biological activity. Moreover, methods of characterizing the capacity of a portion of such an antibody and/or a derivative of such an antibody to bind PF4/heparin and/or to participate in platelet activation, are disclosed in the specification as filed, including but not limited, the methods and assays disclosed in Examples 1-2 of the specification as filed, and/or such methods are known to those skilled in the art and the practice of such methods is routine in the art and should not be considered an undue burden.

There is no requirement under the current law of enablement that each embodiment be reduced to practice. *Amgen Inc. v. Chugai Pharm. Co.*, 18 USPQ2d 1016, 1027 (Fed. Cir. 1991), cited by the Examiner. *Amgen v. Chugai* made clear that that enablement does not require working examples for each species encompassed by a claim under 35 U.S.C. §112, first paragraph. *Accord In re Robbins*, 166 USPQ 552 (CCPA 1970).

Applicants respectfully submit that *Amgen v. Chugai* is not even relevant under the facts of the present application since the *Amgen* Court analyzed the enablement requirement in the context of a claim for all nucleic acids encoding analogs of erythropoietin (EPO) based on disclosure of only a partial amino acid sequence of human EPO. That is, the claim at issue in *Amgen* was similar to that in *Eli Lilly* in that the claim recited DNA sequences where the specification only disclosed an amino acid sequence. Discussing the lack of enablement under 35 U.S.C. §112, first paragraph, the *Amgen* Court noted:

> In affirming the district court's invalidation of claims 7, 8, 23-27, and 29, under Section 112, we do not intend to imply that generic claims to genetic sequences cannot be valid where they are of a scope appropriate to the invention disclosed by an applicant. That is not the case here, where Amgen has claimed every possible analog of a gene containing about 4,000 nucleotides, with a disclosure only of how to make EPO and a very few analogs. *Amgen,* 18 USPQ2d at 1027 (emphasis added).

The holding of *Amgen* is inapplicable under the facts set forth herein. That is, the instant specification discloses the nucleic and amino acid sequences of a monoclonal antibody with the desired biological activity (KKO) and one which does not (RTO). Further, unlike EPO, there is extensive sequence data regarding a monoclonal antibody of the invention including the identification by Applicants of the regions of the proteins that mediate PF4/heparin

binding. Moreover, there are several assays used to determine the biological activity of such a monoclonal antibody, which are set forth in the specification and/or are well-known in the art.

Applicants have disclosed sufficient data to support claims reciting nucleic acids encoding KKO and the functional regions of the monoclonal antibody required for binding with PF4/heparin. Indeed, even though not even a single working example is required for enablement under 35 U.S.C. §112, first paragraph, Applicants have extensively reduced their invention to practice. That is, the specification as filed discloses nucleic acids encoding KKO heavy and light chains (SEQ ID NOs:3 and 4), amino acid sequences of the heavy and light chains for KKO and RTO (SEQ ID NOs:1, and 2 and 11, 12, 13, and 14 as added herein), where the monoclonal antibody specifically binds with PF4/heparin and where the monoclonal antibody activates platelets. Indeed, the specification at Examples 1 and 2 discloses extensive reduction to practice of the present invention, including, but not limited to, numerous assays for detecting binding of a monoclonal antibody capable of binding with a PF4/heparin complex, assays for assessing such monoclonal antibody activity, and methods of measuring the ability of such a monoclonal antibody to activate platelets. Indeed, the specification discloses a hybridoma and nucleic acid and amino acid sequences of such an antibody (specification at pages 43-56, Examples 1 and 2, and Figures 1-8). The specification discloses general characteristics that describe a genus such as the various assays used to characterize the biological activity of the monoclonal antibody. Thus, the skilled artisan would be able, without undue experimentation, to determine whether a monoclonal antibody possesses the requisite biological activity.

Further, it is clear that the level of skill in the art would allow an artisan to easily query numerous hybridomas based on the known biological activity disclosed in the specification as filed, to identify and characterize candidate monoclonal antibodies capable of specifically binding with PF4/heparin and capable of activating platelets as defined and disclosed by Applicants. One skilled in the art of hybridomas and monoclonal antibodies for those possessing a desired biological activity typically engaged in this type of experimentation at the time the application was filed. This is important since the present case law regarding enablement under 35 U.S.C. §112, first paragraph, allows significant experimentation without finding it undue if the art typically engages in such experimentation.

Under the present law of enablement, claims reciting large numbers of species are allowable without disclosure of every species so long as the art engages in experimentation to identify the operative species encompassed by the generic claim. In *In re Vaeck*, 20 USPQ2d 1438, 1445 (Fed. Cir. 1991), reviewing an enablement rejection of a broad claim reciting methods for producing insect proteins in cyanobacteria, the Court of Appeals for the Federal Circuit discussed enablement in the context of generic species claims:

> we do not imply that patent applicants in art areas currently denominated as "unpredictable" must never be allowed generic claims encompassing more than the particular species disclosed in their specification. It is well settled that patent applicants are not required to disclose every species encompassed by their claims, even in an unpredictable art. *In re Angstadt*, 537 F.2d 498, 502-03, 190 USPQ 214, 218 (CCPA 1976). However, there must be sufficient disclosure, either through illustrative examples or terminology, to teach those of ordinary skill how to make and how to use the invention as broadly as it is claimed. This means that the disclosure must adequately guide the art worker to determine, without undue experimentation, which species among all those encompassed by the claimed genus possess the disclosed utility.

In re Vaeck, 20 USPQ2d at 1445 (emphasis added). Thus, not every species need be disclosed where one skilled in the art would be able, without undue experimentation, to determine which species possess the disclosed utility. *See also In re Druey*, 145 USPQ 219, 221 (Bd. Pat. App. & Int. 1965)("The fact that not all possible substituents encompassed by the generic language are illustrated does not preclude appellants from asserting the genus when no reasons have been advanced by the examiner to rebut appellants' assertion that all the compounds embraced by the genus will in fact have the properties ascribed to them.").

The MPEP at § 2164.08(b), discussing inoperative subject matter, states:

> The presence of inoperative embodiments within the scope of a claim does not necessarily render a claim non-enabled. The standard is whether a skilled person could determine which embodiments that were conceived, but not yet made, would be inoperative or operative with expenditure of no more effort than is normally required in the art. *Atlas Powder Co. v. E.I. du Pont de Nemours & Co.*, 224 USPQ 409, 414 (Fed. Cir. 1984) (prophetic examples do not make the disclosure nonenabling.

> . . . A disclosure of a large number of operable embodiments and the identification of a single inoperative embodiment did not render a claim broader that the enabled scope because undue experimentation was not involved in determining those embodiments that were operable. *In re Angstadt*, 190 USPQ 214, 218 (CCPA 1976).

Thus, inoperative embodiments do not necessarily render a claim nonenabled as long as the experimentation required to identify the operative species is not undue.

In the landmark enablement case of in *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988), the court discussed the adequacy of disclosure with regard to a patent disclosing an immunoassay method for the detection of hepatitis B antigen using monoclonal antibodies. The *Wands* Court noted that of 143 hybridomas produced, only nine were assayed and, of those, only four hybridomas secreted IgM antibodies and exhibited a binding affinity constant for the HBsAg determinants of at least 10^9 M^{-1}, a "respectable 44 percent rate of success." *In re Wands*, 8 USPQ2d at 1406. Finding the claims were enabled, the *Wands* Court stated:

> Wands' disclosure provides considerable direction and guidance on how to practice their invention and presents working examples. There was a high level of skill in the art at the time when the application was filed, and all of the methods needed to practice the invention were well known.
>
> The nature of monoclonal antibody technology is that it involves screening hybridomas to determine which ones secrete antibody with desired characteristics. Practitioners of this art are prepared to screen negative hybridomas in order to find one that makes the desired antibody. No evidence was presented by either party on how many hybridomas would be viewed by those in the art as requiring undue experimentation to screen.

In re Wands, 8 USPQ2d at 1406 (emphasis added). Therefore, where, as here, the art typically screens hybridomas and monoclonal antibodies for the desired activity and/or properties, *e.g.*, capable of binding with PF4/heparin and/or activating platelets, where the specification discloses a specific antibody such as KKO and its nucleic acid and amino acid sequences, and where the protein domains mediating binding with PF4/heparin have been identified (*see, e.g.*, specification at pages 43-56, Examples 1 and 2, and Figures 1-8), demonstrating extensive reduction to practice, one skilled in the art would not require undue

experimentation to produce the claimed monoclonal having the desired biological function. Thus, where one skilled in the art routinely screens hybridomas and monoclonal antibodies, having to do so is not the undue experimentation proscribed by 35 U.S.C. § 112, first paragraph, under the reasoning of *In re Wands*.

In *In re Angstadt*, 190 USPQ 214 (CCPA 1976), the court addressed the level of experimentation in an unpredictable art, *i.e.*, the chemical arts, where the claimed invention involved a method of catalytically producing hydroperoxides where the specification admitted that not all disclosed complexes produced the hydroperoxides. The *Angstadt* Court, holding that the invention as claimed was enabled, reasoned:

> We note that many chemical processes, and catalytic processes particularly, are unpredictable. . . .
>
> Appellants have apparently not disclosed every catalyst which will work; they have apparently not disclosed every catalyst which will not work. The question, then, is whether in an unpredictable art, section 112 requires disclosure of a test with every species covered by a claim. To require such a complete disclosure would apparently necessitate a patent application or applications with "thousands" of examples or the disclosure of "thousands" of catalysts along with information as to whether each exhibits catalytic behavior resulting in the production of hydroperoxides. More importantly, such a requirement would force an inventor seeking adequate patent protection to carry out a prohibitive number of actual experiments. This would tend to discourage inventors from filing patent applications in an unpredictable area since the patent claims would have to be limited to those embodiments which are expressly disclosed. A potential infringer could readily avoid "literal" infringement of such claims by merely finding another analogous catalyst complex which could be used in "forming hydroperoxides."

In re Angstadt, 190 USPQ at 218 (emphasis added) (citations omitted). Similarly, in *In re Bundy*, 209 USPQ 48, 52 (CCPA 1981), the court noted the public policy reasons mitigating against imposing a requirement that each compound be tested before a generic species claim would is allowed:

> Early filing of an application with its disclosure of novel compounds which possess significant therapeutic use is to be encouraged. Requiring specific testing of the thousands of prostaglandin analogs encompassed by the present claim in

> order to satisfy the how-to-use requirement of § 112 would delay disclosure and frustrate, rather than further, the interests of the public.

Thus, where methods for assessing whether a monoclonal antibody having the utility of the claimed monoclonal antibodies are well-known in the art and/or disclosed in the specification, and where the nucleic acid sequences of the heavy and light chains for such an antibody are known (*e.g.*, KKO; SEQ ID NOs:3 and 4; Figure 7), as are amino acid sequences (*i.e.*, SEQ ID NOs:1 and 2, Figure 7 and newly added SEQ ID NOs:11 and 13, Figure 6), are disclosed, it would not be undue experimentation to screen hybridomas and monoclonal antibodies which have the disclosed utility where the art typically engages in such experimentation.

More recently, in *Ex parte Mark*, 12 USPQ2d 1904 (Bd. Pat. App. & Int. 1989), the Board reversed the Examiner's rejection for lack of enablement under 35 U.S.C. § 112, first paragraph, with regard to an application involving admittedly "innumerable" muteins comprising a non-essential cysteine which exhibit biological activity after modification to substitute the cysteine. In reversing the Examiner, the *Mark* Court stated:

> To the extent that the examiner is concerned that undue experimentation would be required to determine other proteins suitable for use in the present invention, we find [an applicant]'s declaration to be persuasive that only routine experimentation would be needed for one skilled in the art to practice the claimed invention for a given protein. The fact that a given protein may not be amenable for use in the present invention in that the cysteine residues are needed for the biological activity of the protein does not militate against a conclusion of enablement. One skilled in the art is clearly enabled to perform such work as needed to determine whether the cysteine residues of a given protein are needed for retention of biological activity.

Ex parte Mark, 12 USPQ2d at 1907. Therefore, where one skilled in the art routinely assays the compounds (*e.g.*, hybridomas, monoclonal antibodies, nucleic acids and amino acids encoding the monoclonal antibody chains) for the asserted utility (*e.g.*, binding with PF4/heparin and activating platelets), it is not undue experimentation for them to do so.

Thus, where one skilled in the art would have routinely produced and assessed hybridomas and monoclonal antibodies and proteins encoded by a nucleic acid of interest,

including derivatives thereof, based on a known sequence and identified any monoclonal antibodies having a desired biological activity (*e.g.*, such as being capable of specifically binding with PF4/heparin and activating platelets) following the teachings of the disclosure provided in the specification as filed, such experimentation would not have been undue even if it was complex and even if it entailed "fishing" out the pertinent molecules from among non-pertinent molecules. Armed with the teachings of the instant invention, including that the pertinent monoclonal antibodies bind with a PF4/heparin complex and are involved in activating platelets, and given the knowledge and skill of one skilled in the art, the routineer would not have had to engage in any undue experimentation to practice the invention commensurate with the scope of claims 1-6 and 12-14, and these claims are therefore enabled under 35 U.S.C. §112, first paragraph.

At page 7, line 19 to page 8, line 5 of the Office Action, the Examiner asserts that with particular regard to claim 2, Applicants disclose that the relevant antibodies bind to complexes of PF4 with glycosaminoglycans other than heparin (citing bridging pages 23-24) in the absence of PF4 and that without further written description and guidance, one would have no assurance of obtaining an antibody with the desired property of specifically binding to a glycosaminoglycan other than heparin in the absence of PF4.

Applicants respectfully submit that the Examiner's assertion that the monoclonal antibody binds with glycosaminoglycan other than heparin in the absence of PF4 is not a correct interpretation of the claim. However, Applicants, while not necessarily agreeing with the Examiner's reasoning have amended claim 2 to expedite prosecution of the application. The claim as amended merely clarifies claim 2 as originally written and in essence recites the embodiment of the invention as recited on page 23, line 30 to page 24, line 1, namely that the monoclonal antibody of the invention is also capable of binding specifically with a complex of PF4 and a glycosaminoglycan which is not heparin.

As further described on page 24 or the specification, a series of glycosaminoglycans is provided, including chondroitin sulfates A, B, and C, heparan sulfate, dextran sulfate and low molecular weight heparin. The various glycosaminoglycans cited, as well as others not cited, can be used in assays similar to the assays described for heparin (Figures 1, 2, 4, 5, and 8 and Examples 1 and 2). In fact, Figure 2 depicts the results of the

reactivity of the murine monoclonal antibody KKO to five different PF4/glycosaminoglycan complexes and reactivity was demonstrated for all five. Thus, the skilled artisan would be able, without undue experimentation, to determine using such an ELISA whether PF4 complexed to a glycosaminoglycan other than heparin can bind to a monoclonal antibody of the invention.

Applicants submit that the amendment to claim 2 overcomes the rejection under 35 U.S.C. § 112, first paragraph and that the amendment is fully supported by the specification and claims as filed and introduces no new subject matter.

In sum, claims 1, 2 as amended, 3-6, and 12-14, are enabled by the disclosure provided in the specification as filed as required under 35 U.S.C. §112, first paragraph. Therefore, Applicants respectfully request that the rejection of these claims be reconsidered and withdrawn.

Rejection of Claims 1-6 and 12-14 pursuant to 35 U.S.C. § 112, second paragraph

Claims 1-6 and 12-14 stand rejected under 35 U.S.C. § 112, second paragraph, as being indefinite. In the Examiner's opinion, in claims 1-6 and 12-14 the phrase "the binding . . . with either PF4 or heparin alone" lacks antecedent basis and that the acronym "PF4" should be defined at least in the independent claims as "platelet factor 4 (PF4)".

Applicants, while not necessarily agreeing with the Examiner's reasoning, in a good faith effort to expedite prosecution of the application, have amended independent claims 1 and 12 recite "platelet factor 4".

Next, the Examiner asserts that in claim 3, "the" presence lacks antecedent basis. Applicants, while not necessarily agreeing with the Examiner's reasoning, in a good faith effort to expedite prosecution of the application, have amended claim 3.

The Examiner also asserts that in claims 4 and 13, "homology" should be "sequence identity". Applicants, while not necessarily agreeing with the Examiner's reasoning, in a good faith effort to expedite prosecution of the application, have amended claims 4 and 13 to recite "sequence identity".

Lastly, the Examiner asserts that claims 5 and 14 are indefinite because it is not clear if the parenthetical recitation of "(KKO)" is intended as a limitation of the invention to

this antibody or if the recitation thereof is merely exemplary of encompassed subject and asserts that "the" heavy chain and "the" light chain lack antecedent basis.

Applicants, while not necessarily agreeing with the Examiner's reasoning, in a good faith effort to expedite prosecution of the application, have amended claims 5 and 14 by deleting "KKO" and have added dependent claims 40 and 41 reciting KKO (depending from claims 5 and 14, respectively). The amendments and newly added claims do not add new subject matter and are fully supported by the specification and claims as filed. In addition, Applicants have amended claims 5 and 14, replacing "the" with "a" preceding heavy chain and light chain.

Applicants assert that these amendments are fully supported throughout the specification and claims as filed and introduce no new subject matter. Applicants respectfully submit that claims 1-6 and 12-14 (as amended) and newly added claims 40 and 41, are not indefinite under 35 U.S.C. § 112, second paragraph, thus Applicants request that the rejection of claims 1-6 and 12-14 be reconsidered and withdrawn.

Rejection of Claims 1-6 pursuant to 35 U.S.C. § 103(a)

Claims 1-6 stand rejected under 35 U.S.C. § 103(a) as being, in the Examiner's view, obvious and unpatentable over Amiral (U.S. Patent No. 5,466,582) in view of Blank (1997, Clin. Exp. Immunol. 108:333). The Examiner contends that Amiral discloses detection of antibodies specific for complexes of a heparin drug with PF4 as diagnostic of heparin-induced thrombocytopenia. It is also the view of the Examiner that Amiral teaches that antibodies can be detected by a competitive method using a labelled anti-antigen antibody, and that the anti-antigen antibody can be monoclonal. The Examiner also asserts that Blank teaches the elicitation in mice of antibodies to heparin drug-PF4 complexes which mimic certain properties of heparin-induced thrombocytopenia patient antibodies. Applicants respectfully traverse this rejection and assert that it would not have been *prima facie* obvious for one of ordinary skill in the art at the time the invention was made to use Amiral in view of Blank to obtain the present invention and that the monoclonal antibody as used in the instant application is not an ordinary antibody well known in the art.

Applicants point out that, unlike the present invention which claims a novel composition, i.e., a monoclonal antibody specific for a PF-4/heparin complex, Amiral discloses a diagnostic ELISA assay for detecting antibodies, but does not describe any characteristics of a monoclonal antibody which might be detected by the assay. Blank describes a technique of injecting antibodies to generate anti-idiotype antibodies and Blank's antibodies do not elicit thrombosis, as does a monoclonal antibody of the present invention, nor does their method create an antibody with the specificity of the antibody of the present invention. Thus, Applicants respectfully submit that Amiral in view of Blank does not render claims 1-6 *prima facie* obvious under 35 U.S.C. § 103(a) for the following reasons:

Preliminarily, the three-prong test which must be met for a reference or a combination of references to establish a *prima facie* case of obviousness has not been satisfied in the instant matter. The MPEP states, in relevant part:

> To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all of the claim limitations. MPEP § 2142.

None of these criteria have been met here.

First, Amiral, in view of Blank, does not suggest or motivate modifications of that reference which would render the present invention obvious, nor does it teach or suggest all of the claim limitations. Amiral merely discloses a passive observation and nowhere does Amiral teach or suggest a monoclonal antibody of the present invention. Because Amiral does not suggest or motivate to modify the reference, there can be no reasonable expectation of success in modifying the disclosure of Amiral to arrive at the present invention.

More specifically, claims 1-6 of the present invention relate to a composition comprising a monoclonal antibody which is capable of binding specifically with a PF4/heparin or other PF4/glycosaminoglycan complex. In addition, claim 3 recites that the antibody of the present of the present invention is capable of activating platelets (an indicator

of thrombosis) in the presence of PF4 and heparin, claims 4 and 5 recite specific polypeptide sequences which the antibody comprises, and claim 6 recites the limitation wherein the antibody is a humanized antibody. The combination of references urged by the Examiner does not teach these claim limitations. Amiral relates to the determination of thrombocytopenia induced by an inductor drug (column 2, lines 34-37; column 4, lines 60-61), based on the detection of an antibody in the plasma of the subject (column 2, lines 37-43). Amiral merely states that the assay could be used to detect a monoclonal antibody (column 8, lines 64 to 66), but does not describe characteristics of any monoclonal antibody, such as species specificity, its properties (i.e., causing platelet activation or not; the domain which binds to PF4/heparin), unique heparin dependence, and other antigen-recognizing, all of which are disclosed in the present invention. Amiral's assay is nonspecific, recognizing IgG, IgA, and IgM antibodies. Furthermore, Amiral does not address how to make an antibody that is heparin-dependent and only reactive within a certain dose range of heparin, as is done in the present invention (see Examples 1 and 2 and Figures 1, 2, and 8 of the present application). Therefore, Amiral has nothing whatsoever to do with a monoclonal antibody of the present invention. In light of the foregoing arguments, it is clear that Amiral does not suggest to, or motivate, one of skill in the art to modify the disclosure of Amiral to obtain the present invention. Therefore, there can be no reasonable expectation of success in modifying Amiral to obtain the present invention. That is, one of ordinary skill in the art would not be motivated to modify Amiral, which teaches a method of determining thrombocytopenia by measuring an antibody in the plasma of the subject. Based on the reasoning provided above, Applicants submit that Amiral not only does not teach or suggest the claim limitations of the present invention, it instead teaches away from the claims of the present invention.

Blank does not correct the deficiencies of Amiral. Blank discloses a method of eliciting production of an antibody in vivo by injecting purified antibodies to PF4 and heparin derived from patients with heparin-induced thrombocytopenia/thrombosis (Summary, p. 333; first column, p. 334; Results, p. 335; Figure 2, p. 336). Blank used antibodies from patients and injected them into mice to generate anti-idiotype antibodies, while the present application discloses methods using antigen (PF4/heparin) to generate antibodies. Thus, a very different approach was taken in Blank, compared with the approach of the present invention.

Furthermore, the antibodies generated in Blank do not elicit thrombosis (as measured by platelet activation). In addition, the antibodies of Blank have broad specificity and even recognize beta 2 glycoprotein (see Figure 6), while the antibodies of the present invention specifically bind a PF4/heparin complex or a complex where PF4 complexes with a glycosaminoglycan other than heparin. There is no discussion in Blank concerning compositions comprising monoclonal antibodies. Also, Blank does not disclose specific sequences, while the present invention claims specific heavy and light chain sequences for an antibody of the invention. Thus, Blank is not enabling under the present law and the reference cannot render the sequences of the present invention obvious.

Therefore, Blank has nothing whatsoever to do with a monoclonal antibody of the present invention. In light of the foregoing arguments, it is clear that Blank does not suggest to, or motivate, one of skill in the art to modify the disclosure of Blank to obtain the present invention. Therefore, there can be no reasonable expectation of success in modifying Blank to obtain the present invention. That is, one of ordinary skill in the art would not be motivated to modify Blank, which teaches a method of determining thrombocytopenia by measuring an antibody in the plasma of the subject. Based on the reasoning provided above, Applicants submit that Blank does not teach or suggest the claim limitations of the present invention and in fact teaches away from the present invention.

Further, there would have been no motivation to combine Blank with Amiral to produce the monoclonal antibody of the present invention which binds specifically with a PF4/heparin complex. This is because Amiral and Blank, alone or combined, do not teach or suggest a composition comprising a monoclonal antibody which binds with a PF4/heparin complex or with another glycosaminoglycan, or which can activate platelets, nor do they teach heavy and light chain sequences for a monoclonal antibody, or a humanized derivative thereof, with such binding characteristics. Thus, there was no motivation to combine these references to achieve the surprising results disclosed in the present application,

For the reasons discussed above, Amiral in view of Blank, cannot render claims 1-6 prima facie obvious under 35 U.S.C. §103(a) and, therefore, the rejection should be reconsidered and withdrawn.

Summary

Applicants respectfully submit that each objection and rejection of the Examiner to the present application has been either overcome or is now inapplicable, and that each of claims 1-6 and 12-14, and newly added claims 40 and 41, is now in condition for allowance. Reconsideration and allowance of each of these claims are respectfully requested at the earliest possible date.

Respectfully submitted,
GOWTHAMI M. AREPALLY *ET AL.*

July 13, 2007
(Date)

By: _____

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Enclosures (Amendment Transmittal; Sequence Listing in Paper and Computer Readable Format; Statement to Support Sequence Listing; Marked-up copy of the amended Specification; Marked-up copy of the amended Claims; Revocation and Appointment of Attorney By Assignee; Notice of Change of Address)

MARKED UP COPY OF AMENDED SPECIFICATION

Please amend the specification by deleting the paragraph commencing on page 9, line 28, and ending on page 10, line 4 and inserting the following paragraph in place thereof:

-- Figure 6, comprising Figures 6A and 6B, is a pair of schematics depicting a comparison of the amino acid sequence of the murine monoclonal antibodies KKO and RTO. Figure 6A depicts a comparison of the amino acid sequence of the heavy chain polypeptides of the antibodies. The upper panel of Figure 6A is KKO heavy chain (SEQ ID NO:11) and the lower panel is RTO heavy chain (SEQ ID NO:12). Figure 6B depicts a comparison of the amino acid sequence of the light chain polypeptides. The upper panel of Figure 6B is KKO light chain (SEQ ID NO:13) and the lower panel is RTO light chain (SEQ ID NO:14). Assigned variable region gene families and J-gene segments are as indicated. Amino acid residue numbering and framework (FR) and complementarity-determining region (CDR) designations are per Kabat et al., 1991 ("Sequences of Proteins of Immunological Interest", 5th ed. Bethesda, National Institutes of Health). ">" indicates an amino acid residue encoded by a PCR primer. --

Please amend the specification at page 52 by deleting the paragraph commencing at line 21 and ending on line 29 and inserting the following paragraph in place thereof:

-- The predicted amino acid sequence of KKO, a PF4/heparin complex-specific murine monoclonal antibody, and RTO, a non-heparin dependent anti-PF4 murine monoclonal antibody were compared. Results are shown in Figure 6A and 6B. Sequence analysis revealed the use of very disparate V_H families and J_H-gene segments and V_L families and J_L gene segments for KKO (SEQ ID NOs:11 and 13) and RTO (SEQ ID NOs:12 and 14) heavy and light chains, respectively. Although one cannot rule out similarities in the

idiotopes expressed by two antibodies based on their primary heavy and light chain sequences, it is clear that KKO and RTO are not genetically (or clonally) related, nor do they bear any obvious predicted structural homology to each other. --

Please amend the specification by inserting the following text immediately before the claims at page 56, line 10:

-- Deposit-

Under the terms of the Budapest Treaty on the International Recognition of the Deposit of Microorganisms for the Purpose of Patent Procedure, deposit of a hybridoma, KKO, will be made with the American Type Culture Collection (ATCC) of Manassas, Virginia, USA, where the deposits are given ATCC Accession Numbers _____. The assignee, Science & Technology Corporation @ UNM, represents that the ATCC is a depository afforded permanence of the deposit and ready accessibility thereto by the public if a patent is granted. All restrictions on the availability to the public of the material so deposited will be irrevocably removed upon granting of a patent. The material will be readily available during the pendency of the patent application to one determined by the Commissioner to be entitled thereto under 37 C.F.R. § 1.14 and 35 U.S.C. § 122. The deposited material will be maintained with all the care necessary to keep it viable and uncontaminated for a period of at least five years after the most recent request for the furnishing of a sample of the deposited material, and in any case, for a period of at least thirty (30) years after the date of the deposit or for the enforceable life of the patent, whichever period is longer. Applicant's assignee acknowledges its duty to replace the deposit should the depository be unable to furnish a sample when requested due to the condition of the deposit. --

MARKED UP COPY OF AMENDED CLAIMS

Please amend claims 1, 2, 3, 4, 5, 12, 13, and 14, without prejudice and add new claims 40 and 41 as follows:

1. (Amended) A composition comprising a monoclonal antibody which is capable of binding specifically with a platelet factor 4 (PF4)/heparin complex, wherein said antibody preferentially binds with said PF4/heparin complex relative to [the] said binding with either PF4 or heparin alone.

2. (Amended) The composition of claim 1, wherein said monoclonal antibody is capable of binding specifically with a PF4/glycosaminoglycan [which] complex, wherein said glycosaminoglycan is not heparin.

3. (Amended) The composition of claim 1, wherein said monoclonal antibody is capable of activating platelets [in the presence of] with PF4 and heparin present.

4. (Amended) The composition of claim 1, wherein said antibody comprises a heavy chain polypeptide having an amino acid sequence which shares at least about 80% [homology] sequence identity with SEQ ID NO:1 and a light chain polypeptide having an amino acid sequence which shares at least about 80% [homology] sequence identity with SEQ ID NO:2.

5. (Amended) The composition of claim 1, wherein is said antibody is a murine monoclonal antibody [(KKO)] which comprises [the] a heavy chain polypeptide of SEQ ID NO:1 and [the] a light chain polypeptide of SEQ ID NO:2.

12. (Amended) A method of making a humanized monoclonal antibody which is capable of binding specifically with a platelet factor 4 (PF4)/heparin complex,

wherein said antibody preferentially binds with said PF4/heparin complex relative to [the] said binding of said antibody with either PF4 or heparin alone, said method comprising

a) obtaining a monoclonal antibody which is capable of binding specifically with a PF4/heparin complex, wherein said antibody preferentially binds with said PF4/heparin complex relative to [the] said binding of said antibody with either PF4 or heparin alone;

b) humanizing said antibody in a), whereby a humanized monoclonal antibody is made.

13. (Amended) The method of claim 12, wherein said monoclonal antibody in a) comprises a heavy chain polypeptide having an amino acid sequence which shares at least about 80% [homology] sequence identity with SEQ ID NO:1 and a light chain polypeptide having an amino acid sequence which shares at least about 80% [homology] sequence identity with SEQ ID NO:2.

14. (Amended) The method of claim 12, wherein said monoclonal antibody in a) is a murine monoclonal antibody [(KKO)] which comprises [the] a heavy chain polypeptide of SEQ ID NO:1 and [the] a light chain polypeptide of SEQ ID NO:2.

40. (Newly added) The method of claim 5, wherein said monoclonal antibody is KKO.

41. (Newly added) The method of claim 14, wherein said monoclonal antibody is KKO.